PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.: 09/870,414 Confirmation No.: 7087
Applicants: Usala
Filed: May 30, 2001
Art Unit: 1654
Examiner: Anish Gupta
Title: METHOD OF TREATING CHRONIC ULCERS

Docket No.: 035626/234825
Customer No.: 00826

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PRIOR INVENTION UNDER 37 C.F.R. § 1.131

I, Ronald S. Hill, hereby declare and state that:

1. I am Vice President, Research and Development, for Pioneer Surgical Orthobiologics, Inc., formerly Encelle, Inc., which is the assignee of the present invention. I am empowered to execute this document by the assignee. It is my understanding that, according to MPEP §715.04(I), an assignee may execute a Section 1.131 affidavit where it is not possible to produce an affidavit of the inventor (citing *Ex parte Foster* (Comm'r Pat. 1903)). In the present case, the sole inventor is no longer with the company and it would present a hardship and delay prosecution if the inventor's participation is required.

2. I am aware of WO 00/02999, which was cited by the United States Patent and Trademark Office in the Action dated May 29, 2008. It is my understanding that this document was first published on January 20, 2000.

3. I have firsthand knowledge of events occurring during the time of my employment that evidence both conception and reduction to practice of the present invention

prior to January 20, 2000, in the United States. Specifically, use of the claimed hydrogel matrix to treat a diabetic ulcer was conceived and reduced to practice in the United States prior to January 20, 2000. In support of this statement, attached to the present declaration is the following exhibit, which is a true and accurate copy of an original document with the exception of the redaction therefrom of the dates and of confidential information unrelated to the present application:

> ***Exhibit A*** provides a study report entitled "Cutaneous Ulcer Healing in Dog Secondary to Diabetic Vascular Impairment." The study discussed in this report, which was sponsored by the assignee, was conducted prior to January 20, 2000, and the report itself was prepared by me prior to this date. The study involved treatment of cutaneous skin ulcers in a diabetic dog by injection of E-Matrix™ hydrogel, which is a trade name for a version of the hydrogel matrix that falls within the ranges set forth in Table 1 in the present application. As noted in the report, the application of the matrix material by subcutaneous injection resulted in wound healing. This study formed the basis for Example 1 of the present application, and this example was also described in the related provisional patent application (See Fig. 6 and accompanying discussion in 60/208,116).

4. Accordingly, the attached exhibit provides sufficient evidence of invention, including both conception and reduction to practice, prior to the effective date of the WO 00/02999 reference.

5. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Ronald S. Hill

11/19/2008
Date

EXHIBIT A

STUDY TITLE:

CUTANEOUS ULCER HEALING IN DOG SECONDARY TO DIABETIC VASCULAR IMPAIRMENT

SPONSOR:

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1800 Greene Street
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E-Matrix Treatment Procedures

Table 2 summarizes the treatments performed on each of the six individual cutaneous lesions that developed in dog 11199. E-Matrix was warmed to approximately 37°C immediately before application.

Initial treatments consisted of topical application of E-Matrix (Lesions #1 and #2, [redacted]) or injection of matrix through a catheter sutured into the wound space at the time of surgical closure (Lesion #1, [redacted]). In neither instance did this application route result in improved wound healing. Since matrix is thought to stimulate healing by inducing new blood vessel growth, the matrix in all subsequent treatments was applied by injection into the subcutaneous space circumferentially to the wound margin and across the wound at injections paths 90 degrees to each other. This procedure results in a bed of E-Matrix in the subcutaneous space around the periphery and under the wound. Injection was done using a 20-gauge needle injecting the matrix as the needle was withdrawn. A total of approximately 1 ml of matrix was injected along each 2.5 cm of the needle track. Approximate total injection volumes for each wound is noted in Table 2.

RESULTS

Following E-Matrix injection under the center and circumferentially around the lesions in the subcutaneous space, rapid improvement in the appearance of each wound was noted. Hyperemia was evident over the surface of the wound without swelling or inflammation (Figures 1 and 2). In each instance after E-Matrix injection in all 6 lesions improvement in wound appearance was noted. In some instances the wounds were completely closed within 6 days. For the deepest wound at weight a bearing point, the right front elbow, the wound took longer to resolve. However, even this deep wound eventually was completely closed with new skin and hair growth.

CONCLUSION

In a spontaneously diabetic dog suffering from cutaneous skin ulcer secondary to the diabetes E-Matrix promoted the healing of those lesions that had been refractory to standard wound care. The matrix stimulated hyperemia without edema and swelling. All of the lesions resolved with new skin and hair growth.

INTRODUCTION

Dog #11199 is a spontaneously diabetic mixed breed dog.

The dog was donated to the VA Medical Center on 11 January 1999 as an implant candidate to test Encelle's bioartificial pancreas. The dog has received 4 intraperitoneal injections of porcine organoids between . Following the third intraperitoneal injection abdominal swelling and fever were noted. In addition, cutaneous ulcers formed at 6 distinct locations over 3 weeks. After failure of standard treatment to slow the progression of the cutaneous ulcers in dog 11199, E-Matrix was used to treat the lesions in an attempt improve the clinical condition of the dog. As a result of this failure of treatment, the ulcers were injected with Encelle E-Matrix in an attempt to expedite wound healing. Subsequent to E-Matrix injection all ulcers were resolved with new skin and hair growth.

MATERIALS

All test materials were supplied by the sponsor sterilely packaged in 10 ml syringes.

Test Article:	E-Matrix MF 4109
Identification No.:	Lot # 990611
Storage Conditions:	0-4°C
Test Article Preparation:	The test article was warmed to approximately 37°C by warming in heating pads. Once the E-Matrix was liquefied, it was applied to the wounds by injection with a 19 or 20 gauge needle, injected by cather into the wound site or applied topically by coating a sterile gauze with matrix and applying the gauze to the wound.
Negative Control:	No negative control was used in this study.
Positive Control:	No positive control was used in this study.

METHODS

Test System:

Species:	Canine
Strain:	Mixed Breed
Source:	Donated from Client
Sex:	Female
Body Weight:	Approximately 27 kg

Clinical Summary

Dog 11199 is maintained on a daily regime of a single injection of mixed ultralente and regular insulin. Insulin injections are given in the morning following the initial blood glucose measurement. Food as available ad libitum and consumption monitored daily.

Dog 11199 received 4 intraperitoneal injections of pancreatic tissue suspended in E-Matrix. The injections consisted of a mixture of one volume of pancreatic tissue mixed with 2 volumes of Encelle E-Matrix. Injection dates and volumes were as follows:

Following the third injection the dog experienced abdominal swelling and fever. The first of the cutaneous ulcers were noted on . Standard antibiotic therapy and clinical care resolved the fever and swelling, but failed to resolve the ulcers. Additional lesions became evident during this period. The appearance of the lesions is summarized in Table 1. Until these ulcers appeared, there was no history of cutaneous ulcers in this dog.

Table 1. Cutaneous Lesions in Dog 11199.

Lesion #	Site	First Noted
Lesion #1	Right Front Elbow (RFE)	
Lesion #2	Right Rear Paw (RRP)	
Lesion #3	Right Rear Elbow (RRE)	
Lesion #4	Left Front Elbow (LFE)	
Lesion #5	IP Injection Site (IPIS)	
Lesion #6	Left Rear Leg (LRL)	

Table 2. Treatment of Cutaneous Ulcers in Dog 11199.

Wound #/SITE	Treatment	Treatment Date	Approximate Matrix Volume
Lesion #1 (RFE)	Wound Sutured Closed with Stainless Steel Sutures		NA
	E-Matrix Topical Application[1]		2 ml
	E-Matrix Injected by Catheter into Surgical Site[2]		2 ml
	SS Sutures Tightened; E-Matrix Injected[3]		6 ml
	E-Matrix Topical Application[1]		2 ml
	E-Matrix Injection[4]		8 ml
	Wound Sutured Closed		NA
Lesion #2 (RRP)	E-Matrix Topical Application[1]		2 ml
	E-Matrix Injection[4]		5 ml
	E-Matrix Topical Application[1]		1 ml
Lesion #3 (RRE)	E-Matrix Injection[4]		5 ml
Lesion #4 (LFE)	E-Matrix Injection[4]		5 ml
Lesion #5 (IPIS)	E-Matrix Injection[4]		4 ml
Lesion #6 (LRL)	E-Matrix Injection[4]		4 ml

(1) E-Matrix applied to gauze and the gauze placed over the wound.
(2) Catheter sutured into wound site, E-Matrix was injected and the catheter withdrawn.
(3) Matrix injected in the subcutaneous space circumferentially at wound margin and 2 mm outside wound margin and at 90 degree angles across the wound center.
(4) Matrix injected in the subcutaneous space circumferentially at wound margin and under wound center at 90 degree angles.

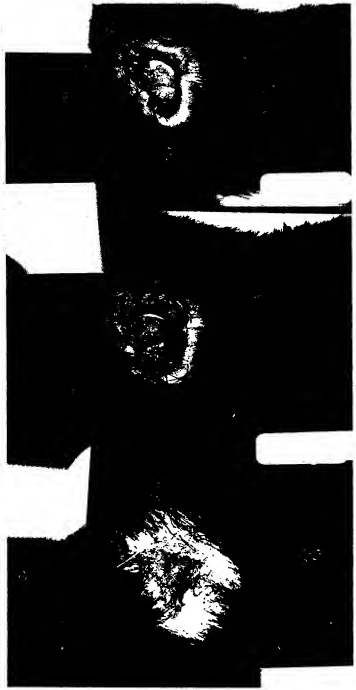

Figure 1. Progression of Wound Healing of Lesion #3, Right Rear Elbow, in Dog 11199.

Figure 2. Progression of Wound Healing of Lesion #2, Right Rear Paw, in Dog 11199.